DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

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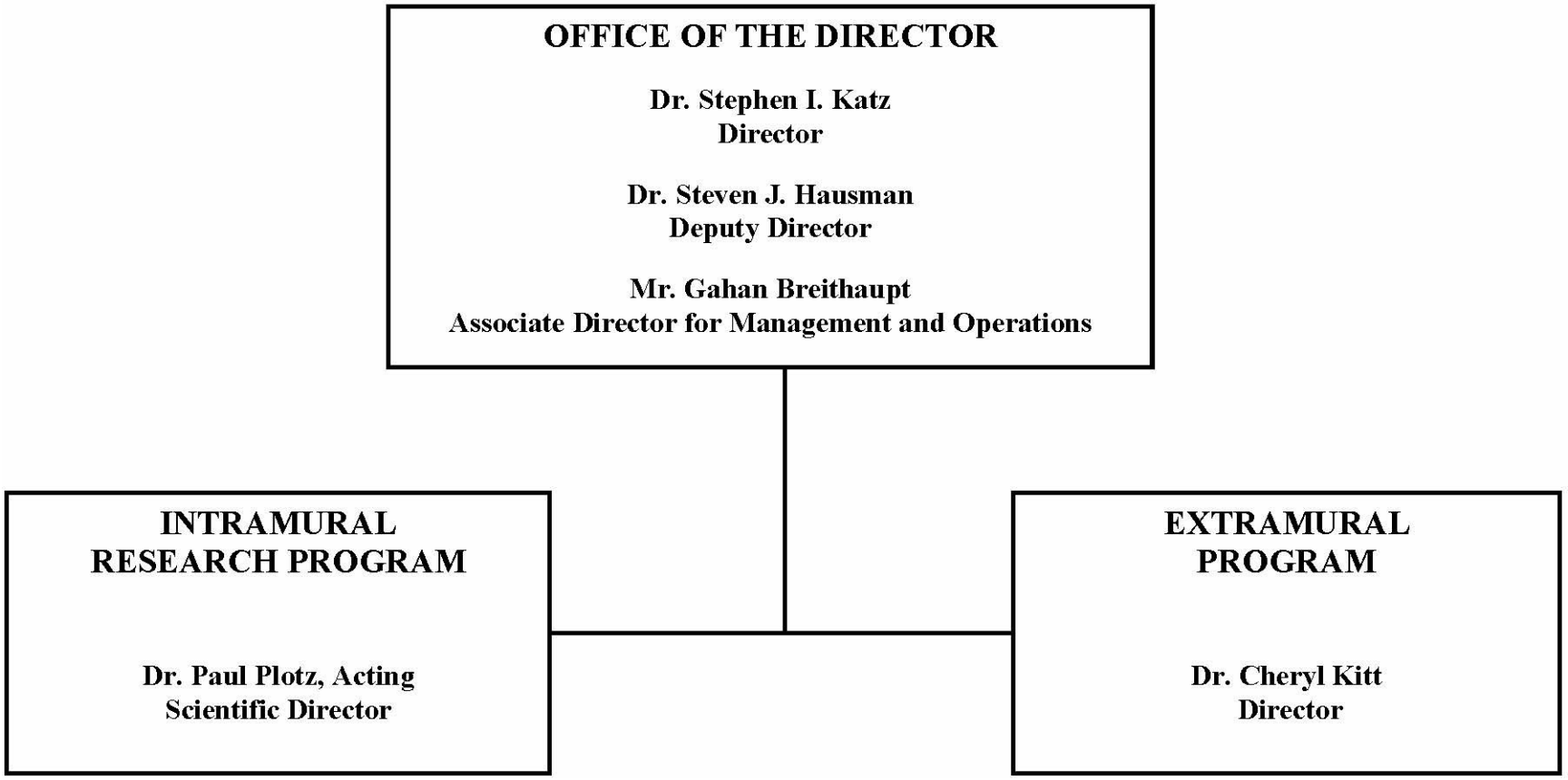
Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to Arthritis and Musculoskeletal and Skin Diseases, [$515,378,000] *$513,063,000*.

[Departments of Labor, Health and Human Services, Education and Related Agencies Appropriations Act, as enacted by the Consolidated Appropriations Act for Fiscal Year 2005]

National Institutes of Health
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Amounts Available for Obligation 1/

Source of Funding	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Appropriation	$504,300,000	$515,378,000	$513,063,000
Enacted Rescissions	(3,234,000)	(4,221,000)	0
Subtotal, Adjusted Appropriation	501,066,000	511,157,000	513,063,000
Real transfer under NIH Director's one-percent transfer authority to other ICs	(1,649,000)	0	0
Comparative transfer to NIBIB for Radiology Program	(32,000)	0	0
Comparative transfer to Buildings and Facilities	(126,000)	0	0
Comparative transfer to/from other NIH ICs for NIH Roadmap	1,649,000	0	0
Subtotal, adjusted budget authority	500,908,000	511,157,000	513,063,000
Unobligated Balance, start of year	0	0	0
Revenue from Breast Cancer Stamp 2/	0		
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	500,908,000	511,157,000	513,063,000
Unobligated balance lapsing	(49,000)	0	0
Total obligations	500,859,000	511,157,000	513,063,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2004 - $376,000 FY 2005 - $1,000,000 FY 2006 - $1,000,000
Excludes $8,000 in FY 2005 and $8,000 in FY 2006 for royalties.

Justification

National Institute of Arthritis and Musculoskeletal and Skin Diseases

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Authorizing Legislation: Section 301 of the Public Health Service Act, as amended.

Budget Authority:

FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
220	$500,908,000	220	$511,157,000	220	$513,063,000	0	$1,906,000

This document provides justification for the Fiscal Year 2006 research activities of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2006 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

INTRODUCTION

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports basic, clinical, and epidemiologic research, research training, and information programs on many of the more common and debilitating diseases affecting the American people. Most of these diseases are chronic and many cause life-long pain, disability and disfigurement. These diseases include the many different forms of arthritis and other rheumatic diseases and numerous disorders of the musculoskeletal system and the skin that affect people of all ages, racial and ethnic populations, and economic strata. Many of the diseases within the mission of the NIAMS have a disproportionate impact on women and minorities. The NIAMS is committed to uncovering the bases of these gender, racial, and ethnic disparities and to devising effective strategies to treat or prevent them.

NIAMS SCIENCE ADVANCES AND NEW INITIATIVES

New Long Range Plan. In 2004, the NIAMS created and launched a process for formulating the next long range plan for the Institute. The current strategic plan is for the period of FY 2000-2004, and the new long range plan will cover the period FY 2005-2009. Planning panels were convened in September and October 2004 in the areas of research on arthritis and other rheumatic diseases, orthopaedics, bone biology and bone diseases, muscle biology and muscle diseases, skin biology and skin diseases, and cartilage and connective tissue biology and diseases. These planning panels included experts from the scientific and lay communities as well as scientists from the NIH Intramural Research Program. In addition, an e-mail note was sent to all

NIAMS grantees and all of the voluntary and professional groups related to the mission areas of the NIAMS inviting their recommendations for scientific areas of needs, opportunities, and gaps. Furthermore, a notice was placed on the NIAMS Web site Home Page inviting suggestions and comments from the public on research needs, gaps, and opportunities. All of this input will be considered as the NIAMS drafts our next long range plan.

New Translational Research Centers. The NIAMS undertook a significant evaluation and planning activity last year. In order to ensure that our Specialized Centers of Research (SCOR) program was taking full advantage of the tremendous opportunities in translational research, the NIAMS formed a panel of experts from across the disciplines in our mission areas and asked these outside experts to evaluate our SCOR program. As a result of their careful analysis and thoughtful report, the NIAMS is phasing out the SCOR program. In FY 2006, the Institute will launch a new mechanism that is known as Centers of Research Translation (CORTs). The new CORTs will pull together basic and clinical researchers in a targeted and organized way, and will put the emphasis on translating research results from basic research to clinical research as well as translating the findings from clinical research to improve and focus the approaches used in basic research – all with the goal of improving public health. The translational studies at these new Centers are expected to maximize the power and benefits of translational research.

The NIH Roadmap for Medical Research. The NIAMS is pleased to partner with other NIH components in the many dimensions of the NIH Roadmap. It has been a little over a year since the NIH Roadmap was launched, and the potential to increase and synergize research at the molecular level and in clinical studies is already being realized. The NIAMS has responsibility for the management of an initiative for a patient-reported outcomes measurement information system – or PROMIS – network, an integral part of the Re-engineering the Clinical Research Enterprise component of the Roadmap. The goal of this initiative is to develop ways to measure patient-reported symptoms such as pain and fatigue and aspects of health-related quality of life across a wide variety of chronic diseases and conditions. One dimension of the PROMIS initiative is to develop a publicly available computerized adaptive test for the clinical research community. Many diseases involve pain, fatigue, and other difficult-to-measure quality of life outcomes, and the development of a test to measure changes in these symptoms will enhance clinical outcomes research and ultimately clinical practice. The Institute will consider ways to enhance the NIAMS-specific dimensions of the PROMIS initiative in FY 2006.

Cross-cutting Areas: Autoimmunity and Behavioral Research. There are a number of disciplines and foci of research that cut across the NIAMS, and indeed much of the NIH. Autoimmunity is one such cross cutting area. While medical research has resulted in significant progress in our understanding of autoimmune diseases, it remains a puzzle why, in some patients, the body's own cells turn against the body’s own tissues. A number of arthritic and skin diseases in the research mandate of NIAMS have their origin in autoimmunity, and research in this area is integral to the Institute. Diseases in this category include systemic lupus erythematosus (SLE or lupus), rheumatoid arthritis, Sjogren's syndrome, alopecia areata, scleroderma, and many blistering skin diseases – all potentially devastating chronic diseases that exact a huge toll in human suffering and economic costs. Active areas of research include studies that are focused on identifying causative agents or components of the body involved in autoimmune disease.

The body has both innate and adaptive immune systems, and they are in a delicate balance with constant interaction. The innate immune system is the series of cells and factors that protect people from a variety of non-specific materials that may enter the body inadvertently. The adaptive immune system relates to the specific responding elements, such as antibody and memory T cells, that arise after immunization and vaccination and increase protection to the particular material to which the individual was exposed. Rather than act separately and sequentially, it has become apparent that there is an interplay between the innate immune system and the adaptive immune system. In order to stimulate research in this area, the NIAMS issued a solicitation to the research community indicating our interest in grant proposals that would increase our understanding of the role of innate immunity in the cause and disease course of autoimmune rheumatic diseases. Understanding the role of the innate immune system in the earlier events in the course of autoimmune diseases could lead to prevention of end organ damage and earlier intervention in autoimmune rheumatic diseases. There was a robust response to this solicitation and the NIAMS funded eight highly meritorious research projects. Autoimmune rheumatic diseases carry significant morbidity and enormous health care costs, and there is great scientific and public health value in identifying new targets for intervention in the early stages of disease. The projects funded in response to this solicitation have the potential to identify such targets.

A second cross cutting area is behavioral research. We know that biopsychosocial perspectives and approaches to research can contribute to our understanding of the etiology, course, and outcomes of rheumatic, musculoskeletal, and skin diseases, but behavioral research in these disorders has been relatively limited. There exists a fundamental need to develop better collaboration among behavioral scientists, physicians, and basic scientists with interests in or relevant to diseases of bones, muscles, joints, and skin. Providing interdisciplinary training opportunities will ultimately enhance the quality and quantity of interdisciplinary research in these diseases. To increase integration of behavioral and biopsychosocial approaches into research on bones, muscles, joints, and skin, the NIAMS issued a solicitation for research in this area, and made awards to three projects that will increase training and career development in biopsychosocial rheumatic, musculoskeletal, and skin diseases research.

The most distressing and disabling aspects of rheumatic and musculoskeletal diseases for most patients are chronic fatigue, pain, and cognitive dysfunction. Behavioral scientists and neuroscientists are uniquely qualified to investigate and develop interventions for these phenomena. Investing in biopsychosocial research is expected to provide new insights into the etiology and course of these diseases, and has great potential to result in more effective approaches to disease prevention and management.

ARTHRITIS AND OTHER RHEUMATIC DISEASES

State-of-the-Art Genomics Project to Examine Gene Expression Patterns in Pediatric Arthritis. The NIAMS has launched a state-of-the-art genomics project that is examining gene expression patterns in children with arthritis, to uncover gene expression patterns that contribute to the development of pediatric arthritis. It is supported by a partnership that includes the NIAMS, a chapter of the Arthritis Foundation, and the Schmidlapp Trust. By using DNA microarrays -- small silicon chips that contain tiny amounts of thousands of known genes -- to

carry out a technique called gene expression profiling, these researchers are analyzing thousands of genes in the blood, fluids and tissues of children newly diagnosed with various types of pediatric rheumatic diseases such as juvenile rheumatoid arthritis or JRA, juvenile ankylosing spondylitis or spinal arthritis, and related immune disorders. Identifying gene expression patterns – groups of genes that are "turned on" – for different types of childhood arthritis will help to improve diagnosis and to predict disease severity for affected children. Gene expression data from four related projects will be stored in a tissue repository and analyzed in a gene informatics center. Storage and analysis of genetic information will help to create a large-scale database that will be a key factor in identifying disease pathways and developing new therapies for pediatric rheumatic diseases. The information learned from this study, including creating a national genome expression database available to the entire scientific community, will accelerate research discoveries in pediatric arthritis.

Scientists Find Gene Variant That Increases Susceptibility to Juvenile Rheumatoid Arthritis. A genetic variation within the interleukin-6 (IL-6) gene increases susceptibility to systemic juvenile rheumatoid arthritis (JRA), according to researchers funded by the NIAMS and the Arthritis Research Campaign. Researchers from around the world collaborated to collect DNA samples from children with JRA and from one or both parents. The transfer of genetic information from parent to child was analyzed, and the scientists found that children who developed JRA were more likely to inherit the variant form of the IL-6 gene from their parents. Children who developed systemic JRA at age 5 or older showed significantly higher levels of this variant compared to the children who developed the disease before age 5. These findings suggest that there may be distinct genetic profiles for the disease that result in differences in age of onset and disease severity. Continuing to uncover disease-associated genes may lead to health care providers having clinically useful subgroupings of systemic JRA.

A New Study to Show How Rheumatoid Arthritis Patients Rate Improvement Change. A new clinical study that has recently been launched in the Intramural Research Program of the NIAMS is seeking to determine how people with rheumatoid arthritis evaluate improvements in disease symptoms. The study will examine how much of an improvement in pain, stiffness, function and other symptoms is needed before patients consider the change important. Using these patient-based criteria, doctors will know if a new treatment has a high likelihood of being rated by patients as helpful or not.

Synthetic Peptide May Help Correct Damaging Immune Responses in Rheumatoid Arthritis. Rheumatoid arthritis is an autoimmune disease, and treatment often involves powerful drugs that will suppress the immune system. While these drugs may be able to keep the disease better controlled, in suppressing the immune system, they may leave the patient especially vulnerable to infection. Researchers supported by the NIAMS have found a potential treatment to suppress the abnormal, self-directed immune response that is responsible for rheumatoid arthritis without hampering the body’s ability to fight bacteria and viruses. The treatment is a synthetic peptide – a chain of amino acids – called dnaJP1.

Previously, researchers had found that in rheumatoid arthritis, the immune system is confused by a sequence of amino acids called human leukocyte antigen (HLA) produced on cells’ surfaces during an immune response. In many patients with rheumatoid arthritis, HLA shares a specific,

characteristic sequence of amino acids. In healthy people, HLA works to help keep the body's immune response under control, but in rheumatoid arthritis, the antigen fails to work properly, resulting in an immune response that causes damage. To help prevent that damaging response, researchers focused their study on the protein called dnaJP1 that the body uses to initiate the response. A particular section of that protein – the dnaJP1 peptide – has the same characteristic amino acid sequence as that found in patients with rheumatoid arthritis. By giving patients a synthetic version of the dnaJP1 peptide, the researchers suspected they could teach the immune system to tolerate this specific amino acid chain instead of seeing it as foreign and attacking it.

In an initial study in a group of patients with rheumatoid arthritis, blood tests showed that dnaJP1 resulted in normal immune system responses. The results of this initial study form the basis of a new larger study that will also assess patients' symptoms and evaluate the effects of dnaJP1 on the immune system and physical exams to determine if changes in the immune system result in a reduction in symptoms. The National Institute of Allergy and Infectious Diseases, the Royal Netherlands Academy of Arts and Sciences, and the Dutch Organization for Scientific Research also helped fund this study.

Family Links in Fibromyalgia. Fibromyalgia is a disorder of unknown etiology that is defined as widespread pain of at least 3 months duration in combination with tenderness at 11 or more of 18 specific tender point sites on the body. Additional characteristic symptoms of fibromyalgia include fatigue, sleep disturbance, and morning stiffness. Results of previous family studies have suggested that fibromyalgia might cluster in families, and might cluster together with major mood disorders in families. NIAMS-supported researchers undertook a controlled family study and found that fibromyalgia was strongly aggregated in families. In addition, both tender point count and total muscle pain scores were strongly associated with fibromyalgia in families, and this association was independent of the presence of major mood disorders in the families. Furthermore, an elevated presence of mood disorders was found in the relatives of fibromyalgia patients. Aggregation of fibromyalgia in families suggests that genetic factors may be involved in the etiology of fibromyalgia and in pain sensitivity, and mood disorders and fibromyalgia may also share some of these inherited factors. In November 2004 the NIAMS supported a workshop on fibromyalgia, with a view to the next scientific advances. The workshop provides clinicians with a conceptual grounding of the current state of the science in understanding the factors contributing to fibromyalgia.

A New Study of Hematopoietic Stem Cell Transplantation for Severe, Treatment-Resistant Lupus Launched. Researchers at NIH, under the leadership of the NIAMS Intramural Research Program, have launched a study to determine whether a therapy using transplantation of hematopoietic stem cells, blood stem cells found in bone marrow, can produce long-term remission for patients with severe, treatment-resistant lupus. The study will include a basic research component to examine the roles of various white blood cells, including the two major components of the immune system – T cells and B cells -- in triggering lupus.

Many patients with severe forms of lupus have limited treatment options that may offer only temporary relief of symptoms and no disease regression. For these patients, stem cell transplantation therapy may offer hope for a normal functioning immune system. Severe forms of lupus can devastate patients, causing pain, fatigue, depression, and in some cases, premature

death. Patients who enter this study will have been treated, to no avail, with high doses of immunosuppressant drugs, which decrease immune function. Researchers believe that by combining immunosuppressant treatment with stem cell transplantation, they can create a new immune system that does not attack the body's healthy cells. Researchers in the National Cancer Institute, the National Institute of Neurological Disorders and Stroke, and the National Institute of Diabetes and Digestive and Kidney Diseases are collaborating in this effort.

The Immune System's B Cells are Targeted in Lupus and Rheumatoid Arthritis. After activation and differentiation, B cells become antibody-producing cells. In patients with autoimmune diseases such as rheumatoid arthritis and lupus, some B cells migrate to the inflamed kidneys and the tissue lining the joints, the synovium, and contribute to the inflammatory process. Recent research demonstrates that the depletion of peripheral blood B cells that occurs when an anti-CD20 antibody (rituximab) is given to patients with autoimmune diseases reduces disease activity even though the levels of antibodies produced by B cells in the serum remain unchanged. Studies in which rituximab was given to patients showed that the rituximab-induced B cell depletion resulted in a significant improvement in lupus disease activity even in the absence of substantial reductions of antibody levels. These research reports support the proposition that B cells have an antibody-independent role in the pathogenesis of rheumatoid arthritis, lupus, and other systemic autoimmunity in general, and they can be targeted for therapeutic interventions.

Additional Insights into Molecular Mechanisms of Brain Changes in Lupus Revealed. The manifestations of lupus are diverse – it can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. A team of researchers supported by the NIAMS focused on the involvement of the nervous system in some people with lupus, and reported significant advances in our understanding of the molecular mechanisms involved in changes that can occur in the brains of people with lupus. These researchers previously reported that the antibodies that attack the DNA of people with lupus can also attack molecules that bind a particular neurotransmitter (glutamate) involved in nerve cell activity. These same antibodies can cause death of the nerve cells, and they are present in the fluid of the brain and spinal cord, possibly affecting brain function. While researchers had previously documented cognitive dysfunction in some patients with lupus, it had not been clear what mechanism was involved in this dysfunction. The Institute released a solicitation for applications on neuropsychiatric lupus in an effort to stimulate additional study of the neurological and psychiatric syndromes associated with this chronic disease, including cognitive, behavioral, affective and motor manifestations. One project that was funded through this solicitation has recently reported additional insights into neuropsychiatric lupus. In this research, it was shown that mice can be induced to produce antibodies to a particular receptor on nerve cells in the brain. These antibodies can be measured in the blood. The antibodies do not cause nerve damage unless the blood-brain barrier is broken and the antibodies have access to the brain. When the blood-brain barrier was broken, these antibodies bound to specific areas in the brain and nerve cell death was demonstrated. Behavioral tests in these mice revealed specific cognitive dysfunction as well. Furthermore, if a drug was given that blocked the brain receptor at the time of the breakdown of the blood-brain barrier, no neuronal damage or apparent cognitive dysfunction was evident. These results have defined a mechanism for the occurrence of neuropsychiatric lupus. In addition, the nature of the brain damage caused by these antibodies can be detected without the

need for a brain biopsy. Protecting this brain receptor from the damaging effects of this particular antibody is a novel approach to the treatment of neuropsychiatric lupus that has emerged from this research.

Biomarkers for Lupus. The NIAMS is actively supporting research to identify and validate biomarkers for lupus. For example, the Institute supports the Autoimmune Biomarkers Collaborative Network, a group that is using cutting edge technologies, such as gene expression profiling with DNA microarrays, to develop biomarkers for lupus. These new technologies may assist in the diagnosis of lupus, help physicians better guide and manage therapy, and provide information on the course of disease for lupus patients. In addition, in the fall of 2003, the NIAMS intramural program held a meeting to discuss the development and validation of biomarkers of lupus. Participants included a number of clinical and basic scientists from the lupus research community as well as representatives from the NIH, the FDA, and voluntary organizations. A key focus of the day was discussion of the barriers to biomarker development in lupus. The participants also underscored the need to identify the potential biomarkers for lupus that should be examined, develop methodologies to validate potential biomarkers, identify the infrastructure necessary to identify lupus biomarkers, and develop methods to collect and analyze large amounts of clinical material. It was recognized that biomarkers have significant value in clinical settings in facilitating the development and use of new therapies. The NIAMS Intramural Research Program has initiated a program to identify and validate lupus biomarkers.

Biomarkers for Osteoarthritis. Osteoarthritis is the most common type of arthritis. Researchers have been hampered by the fact that existing indices of osteoarthritis present a sometimes confusing and relatively insensitive index of disease onset and progression. Discovery of new and more sensitive biomarkers for onset and progression of osteoarthritis (such biomarkers could be biochemical or structural but should be related to pain and loss of function in osteoarthritis) is a significant research need, but undertaking such a complex discovery process was beyond the scope of what any NIH institute or pharmaceutical company could undertake alone. The NIAMS partnered with the National Institute on Aging (NIA), several other NIH components, and three pharmaceutical companies in establishing the Osteoarthritis Initiative, a public-private partnership aimed at developing clinical research resources that support the discovery and evaluation of biomarkers and surrogate endpoints for osteoarthritis clinical trials. For the first time, a public-private partnership is bringing together new resources and commitment to help find biological markers for the progression of osteoarthritis. Patient recruitment is actively underway and by the end of FY 2004, more than 1,000 patients had been recruited. All data and images collected will be available to researchers worldwide to help quicken the pace of scientific studies and biomarker identification. It is expected that this consortium can serve as a model for future endeavors that link the public and private sectors.

A second, related initiative is the Osteoarthritis Biomarkers Network**.** To hasten the pace of discovery of molecular biomarkers for osteoarthritis, the NIAMS established this network and awarded grants to institutions in the United States and Sweden. For the first time, researchers who have been individually studying osteoarthritis biomarkers will share clinical, biological and human resources. Through the network, investigators will learn more about joint destruction by identifying and monitoring biomarkers in blood, urine, and joint tissues. It is hoped that this will provide the clues needed to define the stages of disease on a more consistent and reliable basis.

Investigators in the network will work collaboratively and share resources for the development, evaluation, and validation of biochemical markers for osteoarthritis onset, severity, progression, and response to treatment. The goal is also to speed the process for identifying biomarkers so that people at various stages of the disease can be identified before they progress to significant symptoms of pain and joint deterioration.

MUSCULOSKELETAL BIOLOGY AND MUSCULOSKELETAL DISEASES

Scientists Discover HIV Medication May Preserve Bone. For people infected with the HIV virus, treatment with highly active antiretroviral therapy, such as HIV protease inhibitors that block an enzyme used by the virus, has been associated with unexplained bone loss. Scientists funded by the NIAMS have begun to learn how such agents affect bone, and have discovered that one HIV drug — ritonavir — may actually preserve bone. In basic research studies, scientists looked at the impact of ritonavir and another commonly used protease inhibitor, indinavir, on the formation and function of bone-building cells called osteoblasts as well as bone-resorbing cells called osteoclasts. Under normal circumstances, the two types of cells work together in a balanced process to keep bone strong and healthy. But when bone resorption by osteoclasts outpaces bone formation by osteoblasts, the result is that old bone breaks down faster than new bone is being built. Bones begin to lose mass, sometimes to the point that they become brittle and subject to fractures. In HIV patients taking protease inhibitors, the scientists suspected that bone resorption outpaced formation. What their studies revealed was that indinavir did nothing to the bone-resorbing osteoclasts, but ritanovir did. In fact, ritonavir seemed to affect osteoclast differentiation as well as stopping the ability of mature cells to resorb bone. Scientists next tested these findings in an animal model, and they injected parathyroid hormone or PTH (a standard technique to stimulate bone resorption) into a large number of mice. The scientists then gave ritonavir to some of the PTH-treated mice. When they later examined the bones of both groups of mice as well as mice that had neither treatment, they found that, as expected, the mice given parathyroid hormone had more osteoclasts than untreated mice. However, in the mice given ritonavir as well, osteoclasts were shut down. These animal studies suggest that ritonavir is suppressing bone loss. These intriguing studies in animal models provide many promising avenues of research to be pursued in the future to shed light on bone biology and how the balance in bone is altered in various diseases.

Dental X-rays Can Predict Changes in Bone Micro Architecture. Osteoporosis is characterized by low bone mineral content and breakdown of the micro architecture of the bone scaffold that results in increased bone fragility and fracture. There is a need for improved methods for screening for osteoporosis and for those at high risk for subsequent fractures. Recent reports have shown that bony regions of conventional dental radiographs may be useful in the evaluation of bone micro architecture and changes over time can be followed. When these analyses were applied to women with osteoporosis and women without osteoporosis, it was possible to distinguish the bone changes between these two groups. Women with osteoporosis had altered patterns of trabecular bone, the honey comb-like bone found in the jaw and spine and at the end of long bones, compared to those without osteoporosis. This suggests that dental radiographs could provide a reasonable and widely available screening method to assess low bone mineral and micro architectural changes in bone. These methods could also provide a more sensitive tool for evaluating the efficacy of drugs in modification of bone micro architecture.

Genetic Analysis in Mice Reveals New Drug Target for Osteoporosis. Although many genes are already known to influence bone mass, there is strong evidence that other genes, still unidentified, also influence bone mass and fracture risk. Identifying these genes is challenging, especially in human populations, because humans are genetically very diverse. The analysis is simpler in mice, because genetically uniform laboratory strains of mice are available. Much evidence indicates that bone physiology in mice is similar to that of humans. For that and other reasons, there is a good chance that genes identified in mice will serve to identify human genes that have similar physiological roles. Working with two mouse strains that have very different bone mineral density (BMD), scientists have recently found that naturally occurring variation in a gene called *Alox 15* accounts for a significant part of the difference in BMD. By breeding mice from the two strains, researchers had previously generated hybrid mouse strains with a wide range of BMD. Analysis of the hybrid mice suggested that a number of genes could influence BMD, but did not actually identify any of the genes. Now, using recently developed tools for detailed study of gene activity, the investigators have identified one of the genes as *Alox15*, a gene that was not previously recognized as important for the skeleton. Because *Alox15* is known to be involved in the metabolism of certain compounds related to fats, this discovery has implications for how different metabolic pathways interact to affect bone. In fact, drugs have already been developed that interfere with *Alox15* activity, because of the gene's possible involvement in heart disease and other health problems. These drugs were found to prevent bone loss in rats, confirming that *Alox15* has an important influence on bone mass.

The acquisition and maintenance of bone mass are important determinants of the risk for fracture, especially in women after menopause. The discovery that the *Alox15* gene can influence bone mass in mice is a guide to new ways of preserving bone mass in humans. There are two genes in humans with activities similar to that of *Alox15*, suggesting that one or both of these might be valuable therapeutic targets. In addition, the discovery of *Alox15*'s influence on bone mass suggests that a previously unsuspected metabolic pathway may be important for skeletal health. Studies of this pathway could yield additional clues to the prevention of fractures.

Alendronate and Calcitriol Reduce Bone Loss after Heart Transplantation. Researchers comparing the action of these bone active drugs in a clinical trial have found that both reduce the degree of bone loss commonly seen in the first year following transplant surgery. Heart transplant patients have been shown to be particularly at risk for osteoporosis and fractures due to the type of drugs they take to suppress rejection of the new organ. The drug alendronate, however, which reduces the activity of cells that cause bone loss, was judged to be more clinically useful because it is more simple to monitor and doesn't affect the fragile metabolism of the recovering transplant patients. Calcitriol, a synthetic substance similar to vitamin D, helps regulate calcium metabolism in the body but needs to be carefully monitored and may be more difficult to use in patients with complicated medical situations like transplants.

New Research Grants Awarded to Study Mechanisms of Mineralization of Bone. Mineralization of bone is critical for the hardness and strength that support our weight and resist fracture. A number of serious disorders are caused by mineralization defects, particularly affecting children. There is also increasing evidence that variation in the quantity or quality of mineralization is a factor in the increased risk for fracture in older people. Yet the mineralization

process is poorly understood, partly because few biological models reflecting defects in the process have been available. The NIAMS issued a Request for Applications in this area and awarded two outstanding grant proposals in 2004. The newly awarded grants take advantage of recently developed models that have the potential to illuminate the mineralization process. The models are based on genetically modified mice, in which specific genes have been inactivated, with the consequence that the normal mineralization process is disrupted. These investigations seem likely to reveal new aspects of bone formation and maintenance, and may suggest new targets for the development of drugs to treat a variety of bone disorders.

Functional Outcomes Following Trauma-Related Lower Extremity Amputation. Motor vehicle accidents are a common cause of injury and death, and this is particularly true if the victims are either pedestrians or motor cycle riders. Injuries to the legs are especially common, and may require amputation of the injured portion of the leg. Researchers recently followed a group of patients who underwent above-the-knee amputations at a trauma center to study functional status as well as pain, degree of independence in daily tasks, walking and climbing and other measures. There were no significant differences in function between below-the-knee and above-the-knee amputees, except for faster walking speeds in below-the-knee amputees. However, through-the-knee amputees had lower function than the other two groups of amputees, and physicians were less satisfied with the clinical, functional, and cosmetic recovery of patients with a through-the-knee amputation. The results of this study underscore the need for controlled studies that examine the relationship between levels of amputation and functional outcomes in this population, and secondarily, the relationship between the type and fit of prosthetic devices for these respective levels of amputation, and functional outcomes.

Story of Discovery

Medical Research has Resulted in Improved Length and Quality of Life for People with Joint Replacements. Arthritis is a major contributor to impairment of daily functions and disability in affected people, and it accounts for a large proportion of hospitalizations and health care expenditures of the elderly. A major advance in the treatment of joint degenerations is the success of total joint replacements, procedures in which the damaged joint surfaces are replaced with metal and/or plastic components. Studies over the last decade have documented the cost effectiveness of these procedures, and coupling cost savings with the marked improvement in functional abilities and quality of life means that total joint replacements are making a huge difference in the lives of many Americans.

The tremendous success of this procedure is borne out by follow-up studies of patients who have undergone total joint replacements. The NIAMS supported a 25 to 35-year follow-up of patients who received conventional total hip replacements that were cemented and who were less than 50 years old when surgery was performed. This study showed that less than one-third of the original total hip replacements had to be revised or removed, and more than two-thirds of the original group who had a total hip replacement were functioning well years later. A second study determined that the timing of total joint replacement affects clinical outcomes among patients with osteoarthritis of the hip or knee and suggested that total joint replacement in patients should be done early, before patients experience significant decline of function.

NIH Consensus Development Conferences provide vital information to patients and their health care providers regarding joint replacements. While enthusiastically supporting total hip replacement as a cost-effective and quality of life enhancing therapy, a 1994 Consensus Conference on Total Hip Replacement highlighted concerns about loosening of the artificial joint and the effects of the implant on the body. Deterioration of prosthetic implant materials is a major factor limiting the durability and longevity of total hip replacement. Periprosthetic osteolysis -- literally the disappearance of bone around the implant -- is the most frequent complication of joint replacement. The cause appears to be related to the body's inflammatory response to debris from the implants themselves.

This can result in implant loosening, which can be painful, and ultimately can lead to implant failure and necessitate revision surgery. Such surgery is more difficult to perform, is more costly, and has poorer results than the primary replacement. In basic research laboratories, models were developed to study the effects of different wear particles, including titanium and polystyrene, on bone collagen. Research has provided important information on the roles of decreased bone synthesis as well as inflammation in response to implant particles. The Conference served to stimulate research that led to the development of improved cementing techniques, newer fixation techniques for both cemented and cementless implants, and metallurgic processing to lessen the incidence of breaks in the implants. The NIAMS supported a number of basic, clinical, and translational research studies over the last decade to better understand metal release, transport, storage, and excretion of metallic wear debris in patients who have undergone total joint replacement surgery.

A more recent Consensus Development Conference on Primary Total Knee Replacement (December 2003) concluded that for persons suffering from intractable and persistent knee pain and disability, total knee replacement surgery is a safe and cost-effective therapy that restores mobility and alleviates discomfort. Over 20 years of follow-up data indicate that the procedure is successful in the vast majority of patients.

If we look back over the last several decades at total joint replacement, the effectiveness of this treatment is evidence of the success of public and private support of research in many dimensions including biomaterials, biomechanics, and medical implant science. One of the genuine success stories of medical research is the replacement of joints that have degenerated. Hundreds of thousands of affected Americans have benefited from advances in total joint replacements, and the new joints have improved function in daily life, reduced pain, and increased the quality and productivity of their lives.

MUSCLE BIOLOGY AND MUSCLE DISEASES

Fundamental Research on Muscle Biology. Skeletal muscle is necessary for movement and well being. It visibly responds in size and tone to use or disuse. Its characteristics affect how the body uses energy and its demands require adaptations of the cardiovascular system. Chronic inactivity of skeletal muscle is associated with systemic metabolic dysfunction and diseases such as obesity and insulin-resistant diabetes. A major goal of muscle biology research is to understand skeletal muscle as an integrated whole-body system. Current NIAMS-supported research efforts include the combined use of cell physiology, genetic techniques, biophysics, whole animal measurements, and computer modeling to generate fundamentally new theories of how muscular systems are designed and function to maintain health.

Muscular Dystrophy. Muscular dystrophy refers to a group of genetic diseases characterized by progressive weakness and degeneration of the skeletal or voluntary muscles which control movement. The muscles of the heart and some other involuntary muscles are also affected in some forms of muscular dystrophy, and a few forms involve other organs as well. Duchenne muscular dystrophy is the most common form of muscular dystrophy to affect children. It is caused by mutations in the dystrophin gene and results in repeated cycles of muscle damage and insufficient muscle regeneration, leading to gradual replacement of muscle by fibrous tissue.

Gene Therapy Reaches All Damaged Muscles in Muscular Dystrophy Mouse. Researchers supported by the NIAMS have recently reported that a particular method of gene therapy was able to reach all damaged muscles in a muscular dystrophy mouse, with implications for delivering genetic therapy for muscular dystrophy and perhaps other diseases of the muscle or heart. This research showed for the first time a method by which a corrected gene for dystrophin – a protein found in normal muscle tissue -- can be delivered systemically to affected muscles of a mouse with a disease that resembles Duchenne muscular dystrophy. NIAMS funded

researchers found that by giving a single injection of an adeno-associated viral (AAV) vector – this is a viral ""vehicle"" carrying a mini-dystrophin gene – into the bloodstream, they were able to deliver levels of dystrophin that significantly improved muscle function. These included muscles of the heart and legs.

Previous work showed that muscular dystrophy could be prevented from occurring in a mouse model of the disease by replacing the gene for dystrophin, which is defective in people with the Duchenne form of the disease, with a corrected copy of the gene. In addition, injecting a new dystrophin gene into a single diseased muscle could improve the health of that one muscle. However, until now, no one had found a method in which a new gene could be delivered to all muscles of an adult animal, including muscles that had already developed muscular dystrophy. Researcher injected the vector carrying the gene as well as using vascular endothelium growth factor – a molecule that allows the vector to move through the blood vessel walls into the muscles The vascular endothelium growth factor binds to receptors on the surface of cells that line blood vessels and make them more permeable so that viral particles from the blood stream move into muscle and other tissues, bind to cells, and deliver the new dystrophin gene (this gene has been engineered for expression only in skeletal muscle cells). Thus, the researchers were able to get the genes to all of the intended sites -- the damaged muscles in this model of muscular dystrophy.

This finding gives a significant boost to the many efforts to find answers for muscular dystrophy, for which there is no effective treatment. Additional animal model research is needed to determine whether the dystrophy can be completely eliminated. Researchers suspect that the earlier this treatment is introduced, the better the results will be, and this is currently an area of active study. The hope is that this advance can be applied to other muscular dystrophies as well. The Muscular Dystrophy Association partnered with the NIH in funding this research.

Protein May Hold Key to Repair of Damaged Muscles. For people with muscular dystrophies, treatment is usually limited to physical therapy to prevent painful muscle contractures, orthopaedic appliances for support, and orthopaedic surgery to help correct some of the problems caused by the disease. But scientists in the NIAMS Intramural Research Program and their colleagues are actively seeking to develop better options, including treatments to promote the regeneration of damaged muscles.

These researchers have suggested that treatments could be based on a protein called follistatin, which they have discovered plays a critical role in the growth and regeneration of adult skeletal muscle cells, and/or a group of chemicals called histone deacetylase (HDAC) inhibitors that help follistatin do its job. This study revealed that the level of follistatin is significantly elevated in muscle cells when they are treated with HDAC inhibitors. HDAC inhibitors stimulate the formation of mature muscle cells from immature precursor cells. When follistatin levels are reduced, however, HDAC inhibitors no longer stimulate adult muscle growth, the researchers found. The regeneration activities of the HDAC inhibitors appear to function only in skeletal muscle, since follistatin is not stimulated in other cells tested. In animal studies, administering an HDAC inhibitor produced signs of muscle regeneration in regions of injured skeletal muscle tissue. This new study establishes for the first time that follistatin promotes the recruitment and fusion of immature muscle cells to pre-existing adult muscle fibers. These findings suggest that

follistatin is a promising target for future drug development of muscle regeneration. HDAC inhibitors, by stimulating, follistatin, could be pharmacologically useful as stimulants of muscle regeneration.

Other Muscular Dystrophy Programs and Activities. Working in collaboration with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Child Health and Human Development (NICHD), the NIAMS has been actively engaged in continuing to implement the Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (the MD-CARE Act), to boost research and training related to all forms of muscular dystrophy. One item included in the MD-CARE Act was the establishment of a trans-NIH coordinating committee to oversee federal muscular dystrophy research and education activities. The Secretary of HHS selected the Director of the NIAMS to serve as the chair of the new Muscular Dystrophy Coordinating Committee (MDCC) and in September 2004 the MDCC released the Muscular Dystrophy Research and Education Plan for the NIH. The plan was designed as a working document for the entire muscular dystrophy community and includes five major areas: understanding the mechanisms of disease; screening and diagnosis; treatment strategies; living with muscular dystrophy: rehabilitation, quality of life, and psychosocial issues; and research infrastructure needs. In addition to ongoing muscular dystrophy research, in FY 2003, NIAMS, along with NINDS and NICHD, each funded a Muscular Dystrophy Cooperative Research Center. Researchers at the three centers are conducting studies on Duchenne, myotonic, and facioscapulohumeral muscular dystrophy, and investigating therapeutic approaches including stem cell and gene therapy. In a novel public-private collaboration, the Muscular Dystrophy Association agreed to commit additional funds to enhance activities at each of the three Centers funded. In FY 2004, NIAMS, NINDS, and NICHD re-issued the solicitation for cooperative research centers – now known as Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, and expect to fund two to three additional meritorious centers in FY 2005.

Workshop on the Burden of Muscle Diseases. In follow-up to Congressional language, NIAMS, and the NINDS**,** NICHD and the Centers for Disease Control and Prevention, are actively planning a workshop on the burden of muscle diseases that will take place in January 2005. The purpose of the workshop is to identify existing data on the costs and scope of muscle diseases, with a focus on the muscular dystrophies, and to recommend strategies for developing new information sources.

SKIN BIOLOGY AND SKIN DISEASES

There are thousands of skin diseases catalogued to date, and most of them are clinically challenging for patients as well as their health care providers, while some can be devastating and even fatal. Researchers supported by the NIAMS have made great progress in our understanding of basic skin biology as well as understanding the bases for skin diseases.

Identification of Genes Associated with Psoriasis. A team of researchers funded by the NIAMS identified 2 genes on chromosome 17 which are associated with psoriasis. The region between these two genes acts as a binding site for the protein runx1, which normally serves to regulate genes involved in immune reactions. The researchers found that when this region is

altered, susceptibility to psoriasis occurs. This defective regulation may cause an increased activation of T cells, a type of white blood cell that normally helps protect the body against infection and disease. Such activation triggers inflammation and rapid turnover of skin cells in people with psoriasis. It is also possible that the defective regulation could be affecting other cell types in the skin.

New Animal Models of Alopecia Areata. Alopecia areata is a common skin disease that results in intermittent patchy hair loss in the mildest cases to complete loss of all scalp hair. In the past, studies of alopecia areata have been hampered by the lack of a good animal model. Recently investigators have identified a mouse model that spontaneously develops an adult onset form of alopecia areata. This new model has allowed genetic susceptibility studies to be undertaken, and two new regions on chromosomes 8 and 15 were identified. Previous studies of these genes found that one of them corresponded to a human gene involved in autoimmunity, underscoring the autoimmune basis that alopecia areata is thought to have. These studies show that the genetic basis of alopecia areata is not confined solely to the genes involved in autoimmunity, and underscore the necessity of doing wide genomic searches for genes associated with this disease. The availability of this new animal model will allow better identification of the genetic basis of alopecia areata as well as provide a basis for testing potential interventions.

The Genetic and Molecular Basis of Keloids. Keloids are an abnormal form of scarring that disproportionately affects African Americans. These scars can be so large as to be not only unsightly but also may interfere with function. They tend to occur on the upper half of the body particularly on the head, neck, chest, and back which are particularly unfortunate sites with regard to social interaction as well as interference with bodily functions. In addition to being more prevalent and severe in African Americans they have a familial occurrence in all racial groups. In a recent advance, investigators used a technique of looking at all of the genes in humans to look for the particular genes or location of the genes that induce susceptibility to keloids. Using African American and Japanese families, this group was able to demonstrate a statistically significant location for the susceptibility to keloids on chromosome 2 in the Japanese family and on chromosome 7 in the African American family. It is not surprising that more than a single gene or gene position was identified given the heterogeneous nature of this disease.

Other investigators studied the physiologic basis for keloid formation, and they were able to determine that a blood vessel growth factor was likely to be associated with keloid formation. They were also able to determine that this particular blood vessel growth factor was abnormally present in keloids and, surprisingly, this was being produced by the overlying outer layer of skin, the epidermis, rather than by the dermis, the deeper layer of skin in which the abnormal scar was actually growing. This raises the interesting potential of being able to suppress keloid formation by topical application of an inhibitor of this molecule.

Predicting the Outcome in Chronic Wound Healing of the Skin. Chronic wounds in the skin are a major public health problem in the United States and one that is increasing as the population ages. Venous lower leg ulcers, diabetic foot ulcers and decubitus ulcers are major areas of concern and cost. Among the difficulties in dealing with these chronic wounds is trying to predict which wounds will be more difficult to heal and, therefore, should be treated with the advanced and often expensive procedures early, and which other markers of eventual healing can

be substituted for complete closure of the wound in doing studies of new interventions. NIAMS-supported researchers recently designed a study based on existing datasets of over 20,000 individuals with venous leg ulcers to try to determine whether any of several potential prognostic factors correlated best with eventual closure of the ulcer. Other researchers focused on one of the most promising new avenues in the treatment of chronic skin wounds -- the use of a variety of bioengineered skin substitutes. They designed a classification system of both diabetic and venous ulcers that was applied in the evaluation of the healing following the use of a bioengineered skin. The scoring system successfully predicted which wounds would eventually heal completely and which would not. Applying a system like this, once validated, should allow the FDA to accept shorter duration trials with an end point other than complete wound closure which will greatly reduce the cost of such clinical trials.

INFORMATION DISSEMINATION

Information dissemination is a crucial dimension of the NIAMS mandate. If Institute-supported researchers have powerful research results but they are not disseminated to patients and health care providers, these results are of limited value. Institute staff work with voluntary and professional groups across our broad mandate to ensure that patients and health care providers have the latest research-based information. We also work closely with these groups to ensure that we are not duplicating efforts.

The NIAMS is currently developing several unique information tools, including: a CD-ROM for health care professionals on pediatric rheumatic diseases (in partnership with the Arthritis Foundation); a middle school science curriculum about musculoskeletal and skin health (in partnership with the NIH Office of Science Education); and NIH Senior Health web site components on osteoporosis and Paget's disease of bone (with the NIA to complement an arthritis unit we created that is already operational).

NIAMS information dissemination efforts provide outreach in other ways as well: the Institute is working with the Health Resources and Services Administration (HRSA) to distribute NIAMS information packages to hundreds of HRSA's community health centers around the country, and we are exploring a similar distribution to the Indian Health Service's clinics. The NIAMS continues its community-based research initiative called the Health Partnership Program which is done in collaboration with Washington, DC, area community partners in an under-served part of the city, with the goal of helping us understand and address issues of health disparities in rheumatic diseases.

CONCLUSION

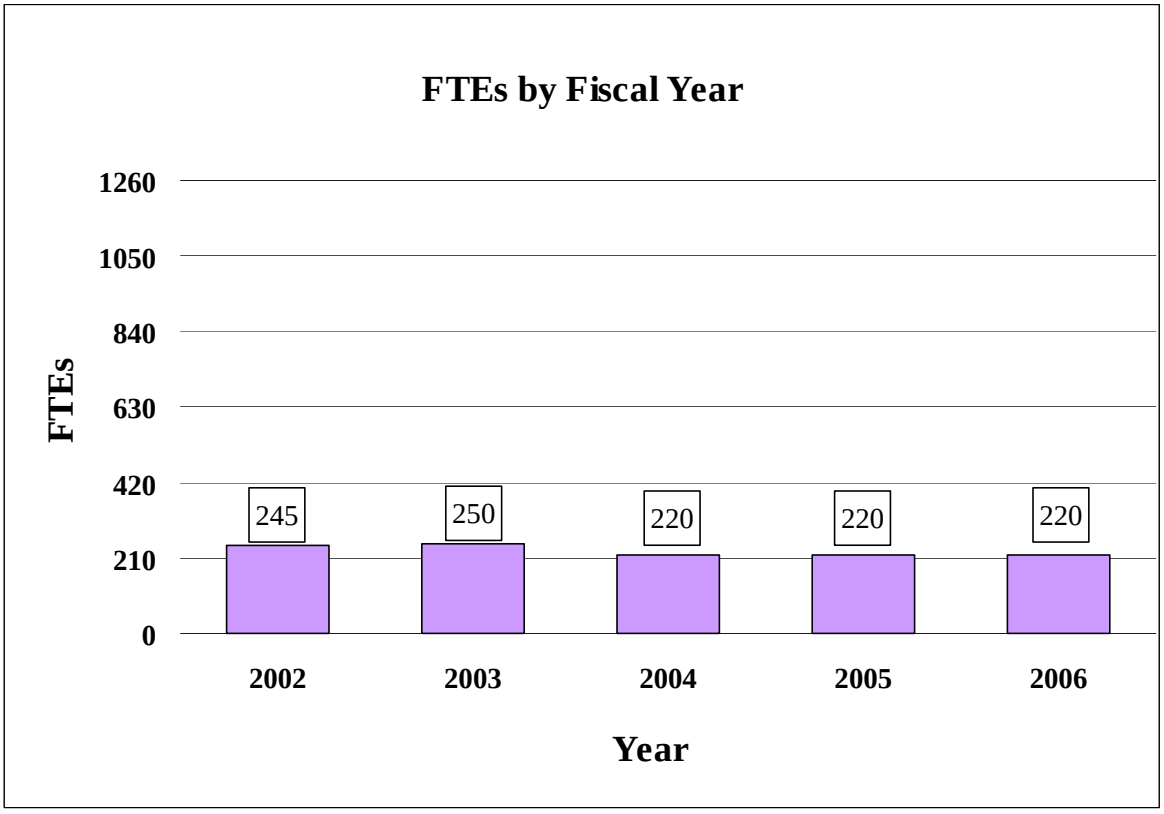
Bones, muscles, joints, and skin are central components of the human body. We now understand better how they develop and function normally, and how they are altered in disease. We now know much more about the roles of genetics, the environment, diet, and behavior in disease. Many chronic diseases affect women and minorities disproportionately, and we continue to actively pursue the causes of these gender and ethnic differences. Perhaps most noteworthy, we are making significant progress in our efforts to prevent disease in the first place. The NIAMS supports scientists who are making significant inroads in developing strategies for chronic

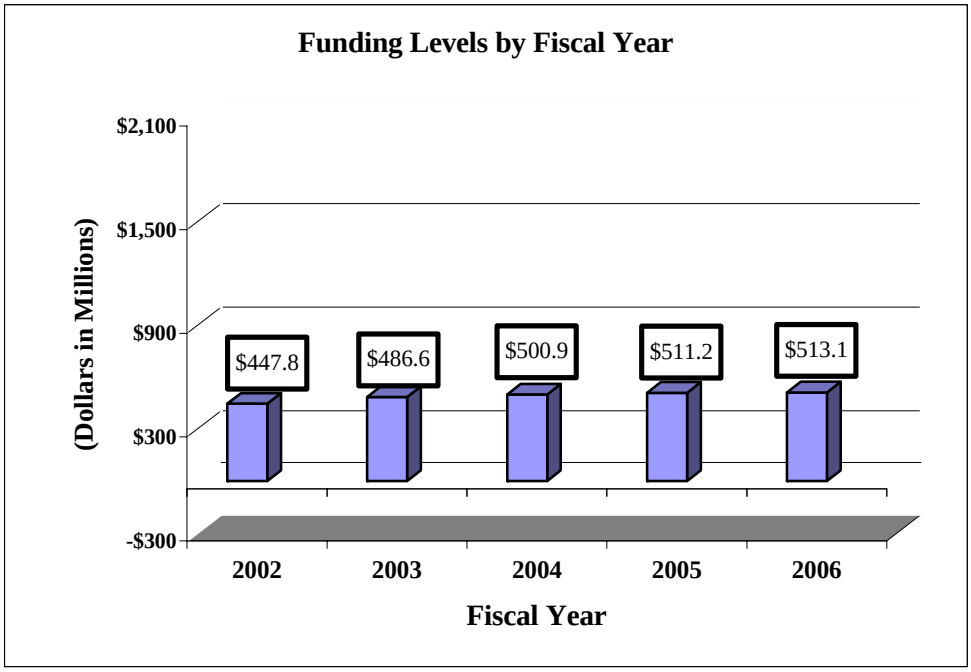
disease prevention, and, as people are living longer lives, they are seeking strategies to maximize their quality of life and minimize the impact of the many chronic diseases that can compromise that quality of life. The research supported by the NIAMS demonstrates that medical research has made a genuine difference in the lives of all Americans.

BUDGET POLICY

The Fiscal Year 2006 budget request for the NIAMS is $513,063,000, an increase of $1,906,000 and 0.4 percent over the FY 2005 Appropriation. Also included in the FY 2006 request, is NIAMS' support for the trans-NIH Roadmap initiatives, estimated at 0.89% of the FY 2006 budget request. This Roadmap funding is distributed through the mechanisms of support, consistent with the anticipated funding for the Roadmap initiatives. A full description of this trans-NIH program may be found in the NIH Overview.

A five year history of FTEs and Funding Levels for NIAMS is shown in the graphs below.



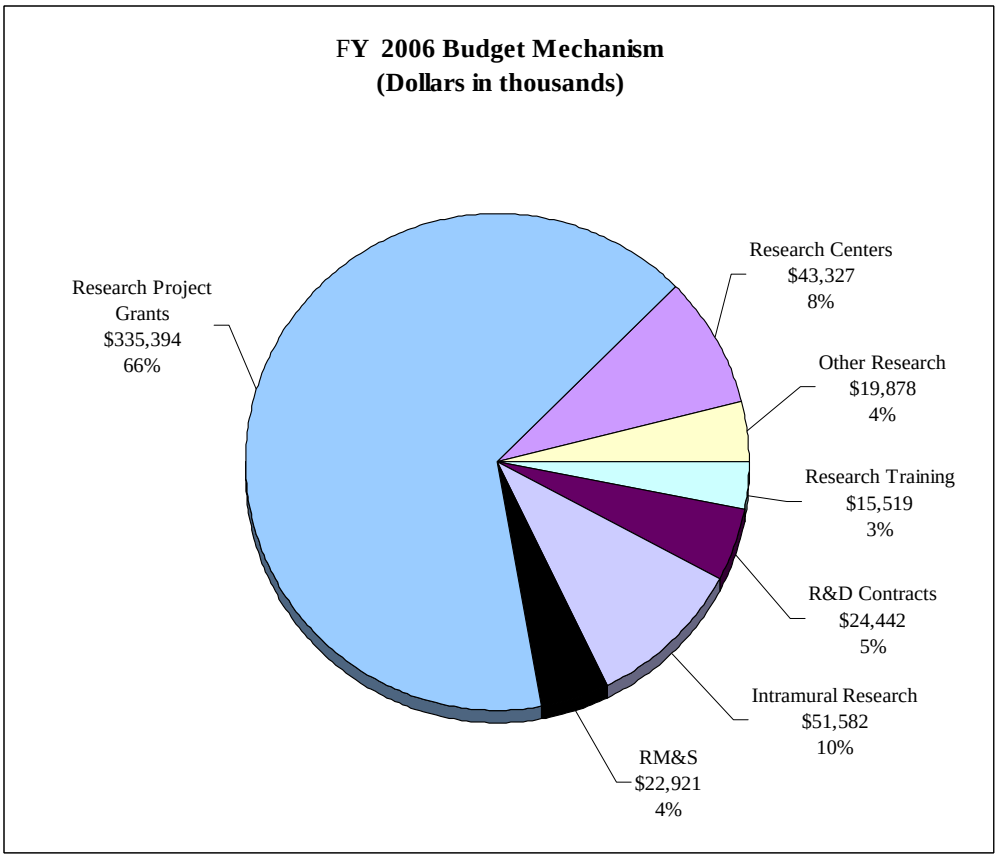


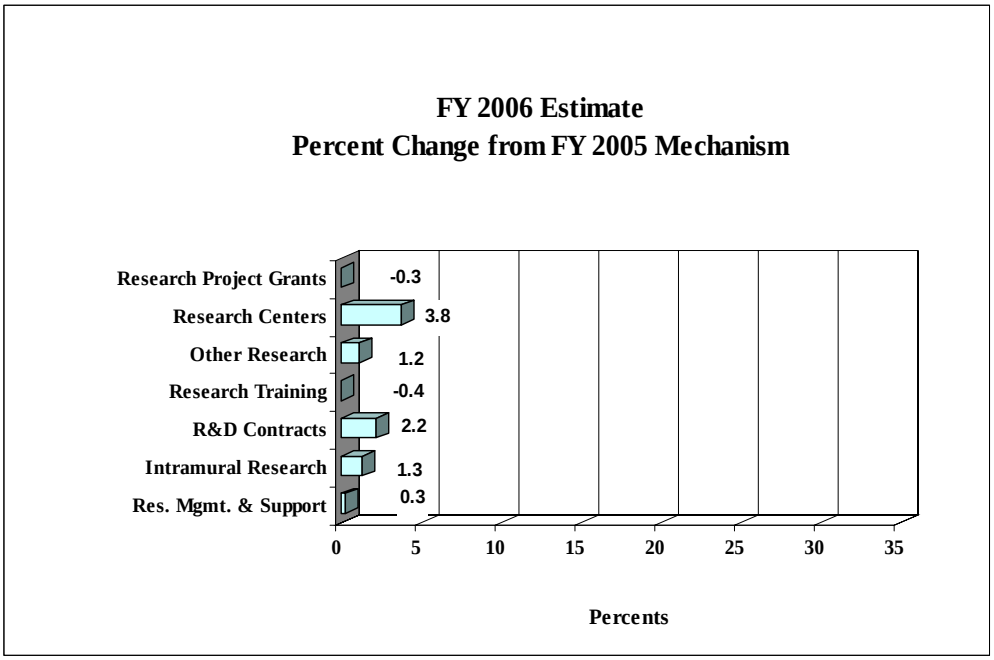
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while pursuing new research opportunities. We estimate that the average cost of competing RPGs will be $298,400 in FY 2006. While no inflationary increases are provided for direct, recurring costs in noncompeting RPGs, where the NIAMS has committed to a programmatic increase in an award, such increases will be provided.

Advancement in medical research is dependent on attracting, training, and retaining the best and the brightest individuals to pursue careers in biomedical and behavioral research. In the FY 2006 request, most stipend levels for individuals supported by the Ruth L. Kirschstein National Research Service Awards are maintained at the FY 2005 levels. To help prevent the potential attrition of our next generation of highly trained post-doctoral trainees, stipend levels for post-docs with 1-2 years of experience are increased by 4.0%. This will bring these stipends closer to the goal NIH established for post-doc stipends in March 2000. In addition, individual post-doctoral fellows will receive an increase of $500 in their institutional allowance for rising health benefit costs. The need for increased health benefits is particularly acute for these post-doctoral trainees, who, because of their age and stage of life are more likely to have family responsibilities. The increases in stipends and health insurance are financed within the FY 2006 request by reducing the number of Full-Time Training Positions, because the NIH believes that it is important to properly support and adequately compensate those who are participating in these training programs, so that the programs can continue to attract and retain the trainees most likely to pursue careers in biomedical, behavioral and clinical research.

The Fiscal Year 2006 request includes funding for 40 research centers, 176 other research grants, including 52 clinical career awards, and 65 R&D contracts. Intramural Research and Research Management and Support receive increases of 0.5 percent, the same as the NIH total increase.

The mechanism distribution by dollars and percent change are displayed below:





NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Mechanism - Total

MECHANISM	FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	760	$251,048,000	745	$250,460,000	752	$247,798,000
Administrative supplements	(25)	1,275,000	(30)	1,599,000	(30)	1,526,000
Competing:						
Renewal	68	27,041,000	66	26,775,000	67	27,347,000
New	176	46,041,000	175	45,607,000	180	46,660,000
Supplements	2	294,000	2	290,000	2	296,000
Subtotal, competing	246	73,376,000	243	72,672,000	249	74,303,000
Subtotal, RPGs	1,006	325,699,000	988	324,731,000	1,001	323,627,000
SBIR/STTR	52	11,737,000	52	11,781,000	52	11,767,000
Subtotal, RPGs	1,058	337,436,000	1,040	336,512,000	1,053	335,394,000
Research Centers:						
Specialized/comprehensive	37	37,725,000	38	41,407,000	39	42,877,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	209,000	0	327,000	1	450,000
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	37	37,934,000	38	41,734,000	40	43,327,000
Other Research:						
Research careers	139	15,981,000	141	16,484,000	142	16,684,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	9,000	0	12,000	0	14,000
Minority biomedical research support	4	1,150,000	5	1,492,000	5	1,492,000
Other	24	1,218,000	29	1,662,000	29	1,688,000
Subtotal, Other Research	167	18,358,000	175	19,650,000	176	19,878,000
Total Research Grants	1,262	393,728,000	1,253	397,896,000	1,269	398,599,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	44	1,988,000	51	2,440,000	50	2,440,000
Institutional awards	255	11,578,000	251	13,148,000	247	13,079,000
Total, Training	299	13,566,000	302	15,588,000	297	15,519,000
Research & development contracts	63	22,474,000	65	23,915,000	65	24,442,000
(SBIR/STTR)	(0)	(23,000)	(0)	(0)	(0)	(0)
	FTEs		FTEs		FTEs	
Intramural research	136	49,045,000	133	50,897,000	133	51,582,000
Research management and support	84	22,095,000	87	22,861,000	87	22,921,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Buildings and Facilities		0		0		0
Total, N	220	500,908,000	220	511,157,000	220	513,063,000
(RoadMap Support)		(1,721,000)		(3,231,000)		(4,584,000)
(Clinical Trials)		(32,536,000)		(33,090,000)		(33,090,000)

NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2004 Actual FTEs	FY 2004 Actual Amount	FY 2005 Appropriation FTEs	FY 2005 Appropriation Amount	FY 2006 Estimate FTEs	FY 2006 Estimate Amount	Change FTEs	Change Amount
Extramural Research:								
Arthritis and Musculoskeletal and Skin Diseases		$429,768		$437,399		$438,560		$1,161
Subtotal, Extramural research		429,768		437,399		438,560		1,161
Intramural research	136	49,045	133	50,897	133	51,582	0	685
Res. management & support	84	22,095	87	22,861	87	22,921	0	60
Cancer Control & Prevention	0	0	0	0	0	0	0	0
Total	220	500,908	220	511,157	220	513,063	0	1,906

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Summary of Changes

FY 2005 Estimate				$511,157,000
FY 2006 Estimated Budget Authority				513,063,000
Net change				1,906,000
	FY 2005 Appropriaton		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$16,902,000		$231,000
b. Annualization of January 2005 pay increase		16,902,000		298,000
c. January 2006 pay increase		16,902,000		156,000
d. One less day of pay		16,902,000		(67,000)
e. Payment for centrally furnished services		9,079,000		45,000
f. Increased cost of laboratory supplies, materials, and other expenses		24,916,000		331,000
Subtotal				994,000
2. Research Management and Support:				
a. Within grade increase		8,909,000		155,000
b. Annualization of January 2005 pay increase		8,909,000		158,000
c. January 2006 pay increase		8,909,000		82,000
d. One less day of pay		8,909,000		(36,000)
e. Payment for centrally furnished services		3,578,000		18,000
f. Increased cost of laboratory supplies, materials, and other expenses		10,374,000		151,000
Subtotal				528,000
Subtotal, Built-in				1,522,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Summary of Changes--continued

CHANGES	2005 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	745	$252,059,000	7	($2,735,000)
b. Competing	243	72,672,000	6	1,631,000
c. SBIR/STTR	52	11,781,000	0	(14,000)
Total	1,040	336,512,000	13	(1,118,000)
2. Research centers	38	41,734,000	2	1,593,000
3. Other research	175	19,650,000	1	228,000
4. Research training	302	15,588,000	(5)	(69,000)
5. Research and development contracts	65	23,915,000	65	527,000
Subtotal, extramural				1,161,000
	FTEs		FTEs	
6. Intramural research	133	50,897,000	0	(309,000)
7. Research management and support	87	22,861,000	0	(468,000)
8. Cancer control and prevention	0	0	0	0
9. Construction		0		0
10. Building and Facilities		0		0
Subtotal, program		511,157,000		384,000
Total changes	220		0	1,906,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Authority by Object

	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	220	220	0
Full-time equivalent of overtime & holiday hours	0	0	0
Average ES salary	$148,974	$152,922	$3,948
Average GM/GS grade	11.4	11.4	0.0
Average GM/GS salary	$76,239	$79,098	$2,859
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$99,614	$102,254	$2,640
Average salary of ungraded positions	101,856	105,676	3,820

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$11,806,000	$12,269,000	$463,000
11.3 Other than Full-Time Permanent	5,654,000	5,869,000	215,000
11.5 Other Personnel Compensation	282,000	292,000	10,000
11.7 Military Personnel	246,000	256,000	10,000
11.8 Special Personnel Services Payments	3,033,000	3,127,000	94,000
Total, Personnel Compensation	21,021,000	21,813,000	792,000
12.0 Personnel Benefits	4,587,000	4,765,000	178,000
12.1 Military Personnel Benefits	176,000	183,000	7,000
13.0 Benefits for Former Personnel	26,000	27,000	1,000
Subtotal, Pay Costs	**25,810,000**	**26,788,000**	**978,000**
21.0 Travel & Transportation of Persons	740,000	720,000	(20,000)
22.0 Transportation of Things	145,000	143,000	(2,000)
23.1 Rental Payments to GSA	0	0	0
23.2 Rental Payments to Others	0	0	0
23.3 Communications, Utilities & Miscellaneous Charges	479,000	481,000	2,000
24.0 Printing & Reproduction	272,000	262,000	(10,000)
25.1 Consulting Services	1,705,000	1,652,000	(53,000)
25.2 Other Services	6,223,000	6,088,000	(135,000)
25.3 Purchase of Goods & Services from Government Accounts	39,625,000	39,806,000	181,000
25.4 Operation & Maintenance of Facilities	483,000	466,000	(17,000)
25.5 Research & Development Contracts	20,076,000	20,578,000	502,000
25.6 Medical Care	563,000	560,000	(3,000)
25.7 Operation & Maintenance of Equipment	1,142,000	1,128,000	(14,000)
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**69,817,000**	**70,278,000**	**461,000**
26.0 Supplies & Materials	5,835,000	5,767,000	(68,000)
31.0 Equipment	1,463,000	1,428,000	(35,000)
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	406,594,000	407,194,000	600,000
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	2,000	2,000	0
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	**485,347,000**	**486,275,000**	**928,000**
Total Budget Authority by Object	**511,157,000**	**513,063,000**	**1,906,000**

NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Salaries and Expenses

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$11,806,000	$12,269,000	$463,000
Other Than Full-Time Permanent (11.3)	5,654,000	5,869,000	215,000
Other Personnel Compensation (11.5)	282,000	292,000	10,000
Military Personnel (11.7)	246,000	256,000	10,000
Special Personnel Services Payments (11.8)	3,033,000	3,127,000	94,000
Total Personnel Compensation (11.9)	**21,021,000**	**21,813,000**	**792,000**
Civilian Personnel Benefits (12.1)	4,587,000	4,765,000	178,000
Military Personnel Benefits (12.2)	176,000	183,000	
Benefits to Former Personnel (13.0)	26,000	27,000	1,000
Subtotal, Pay Costs	**25,810,000**	**26,788,000**	**978,000**
Travel (21.0)	740,000	720,000	(20,000)
Transportation of Things (22.0)	145,000	143,000	(2,000)
Rental Payments to Others (23.2)	0	0	0
Communications, Utilities and Miscellaneous Charges (23.3)	479,000	481,000	2,000
Printing and Reproduction (24.0)	272,000	262,000	(10,000)
Other Contractual Services:			
Advisory and Assistance Services (25.1)	1,705,000	1,652,000	(53,000)
Other Services (25.2)	6,223,000	6,088,000	(135,000)
Purchases from Govt. Accounts (25.3)	14,739,000	14,798,000	59,000
Operation & Maintenance of Facilities (25.4)	483,000	466,000	(17,000)
Operation & Maintenance of Equipment (25.7)	1,142,000	1,128,000	(14,000)
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**24,292,000**	**24,132,000**	**(160,000)**
Supplies and Materials (26.0)	5,827,000	5,759,000	(68,000)
Subtotal, Non-Pay Costs	31,755,000	31,497,000	(258,000)
Total, Administrative Costs	**57,565,000**	**58,285,000**	**720,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

FY 2005 House Appropriations Committee Report Language (H. Rpt. 108-636)

Item

Bone diseases - The Committee encourages NIAMS to support trans-NIH research into all aspects of genetics and gene therapies for the treatment of metabolic bone diseases, the role of environmental and lifestyle factors in bone disease, the effects of depression and cardiovascular disease on bone disease, the impact of mechanical loading of bone, and on bone health and osteoporosis in special groups, such as non-Caucasian ethnic groups. (p. 91)

Action taken or to be taken

The NIAMS leads the Federal research effort in bone diseases, and supports science ranging from very basic studies to clinical and translational projects, as well as early intervention and prevention efforts. The Institute actively collaborates with a variety of Federal and private organizations to advance the field of bone disease research. For example, the NIAMS leads the Federal Working Group on Bone Diseases, an interagency committee that offers a forum for sharing information and facilitating the development of collaborative bone research activities based on each agency's mission. Several other NIH components including the National Institute on Aging, the National Institute of Diabetes, Digestive, and Kidney Disorders, the National Institute of Dental and Craniofacial Research, the National Center for Complementary and Alternative Medicine, and the National Cancer Institute participate in working group activities. Other Federal agencies such as the Agency on Healthcare Research and Quality, Centers for Disease Control and Prevention, Food and Drug Administration, Department of Veterans Affairs, and the Department of Education are also active participants.

In the area of gene- and cell-based research, NIAMS-supported researchers have recently used a combination of mouse breeding and genetic technology to identify a gene that strongly influences peak bone mass in mice. The gene, which is present in humans as well as mice, was not previously known to be involved in bone biology, and hence represents a promising new target for development of drugs that could prevent or reverse the bone loss that leads to osteoporosis.

Research is currently underway to investigate the potential connection between bone health and cardiovascular disease. An ongoing collaboration between NIAMS and NHLBI has yielded significant insights into the parallels between bone formation and the vascular calcification that is a hallmark of cardiovascular disease. In addition, studies of bone mass are revealing the close

connection between bone biology and fat metabolism, long-recognized as a major factor in cardiovascular disease.

The NIAMS supports a broad range of investigations into the response of bone to mechanical loading. These projects include studies of the cellular and molecular mechanisms by which load is detected and translated into new bone growth, as well as efforts to develop therapies that will take advantage of these mechanisms to increase bone mass. Other NIAMS-supported research has shown that specific strength training and resistance exercises can retard and even reverse bone loss in healthy postmenopausal women, and that estrogen replacement is not necessary to gain the benefit of the exercise.

In collaboration with the National Institute on Aging, the NIAMS supports a large study of osteoporosis and other age-related diseases in men, called Mr. OS. This project complements an ongoing study of osteoporotic fractures in women that has been supported by the Institute for over a decade. The Mr. OS effort will facilitate gender comparisons and address the issue of why osteoporotic fractures are more common in women.

Item

Scoliosis - The Committee encourages NIAMS, in coordination with other institutes, to enhance research relevant to scoliosis to identify bio-mechanical causes and to develop genetic strategies to prevent the condition. (p. 91)

Action taken or to be taken

The NIAMS, along with the National Eye Institute and the National Institute on Child Health and Human Development, supports a broad range of research to better understand skeletal development, mechanical properties, and spinal injury and disorders. These diverse scientific studies complement research that is looking directly at scoliosis and how best to diagnose and treat the disease.

The Institute is actively supporting genetics research in the area of scoliosis. For example, the NIAMS supports gene expression studies of early spinal development that aim to identify new genes associated with the development of scoliosis at birth. Other researchers are searching for the genes responsible for familial scoliosis, a complex genetic disorder with limited treatment options.

Exciting work is also being done to better understand the factors that affect skeletal stability and instability in both humans and animals. Using a novel animal model, researchers are looking at how structural stability increases in the developing mammalian backbone. The results of this study should shed light on the causal factors associated with back instability, as well as identify structures that protect the spinal cord from damage. NIAMS also supports the development of new technologies with the potential to improve treatment of skeletal disorders and facilitate repair following trauma to the skeleton.

NIAMS-supported researchers are examining methods for improving spinal visualization, including the development of three-dimensional imaging technologies to allow for detailed analyses of the spine in a moving person, without the risks of radiation associated with traditional x-rays. Related research is being done to adapt methods of topographic surface mapping to examine the back's surface and develop mathematical models to track spine curvatures. These and other novel approaches have the potential to increase the safety and effectiveness of tools used in the management and treatment of scoliosis.

Item

Scleroderma – The Committee is encouraged by NIAMS's growing interest in scleroderma, a chronic and progressive disease that predominantly strikes women. Scleroderma is disfiguring and can be life-threatening, and effective treatments are lacking. The Committee encourages NIAMS to collaborate with other Institutes, including NHLBI, NIAID, NIDDK, and NIDCR, to generate additional research opportunities for scleroderma to identify genetic risk factors and safe and effective treatments. (p. 91)

Action taken or to be taken

Scleroderma is an autoimmune disease, a broad category of diseases in which the body's immune system attacks the body's own tissues as if they were foreign invaders causing significant damage to target organs. The NIAMS continues to work closely with other public and private organizations to advance scleroderma research. For example, NIAMS, along with NHLBI, NIDDK, and NIDCR, is an active member of the NIH Autoimmune Diseases Coordinating Committee (ADCC), which is led by the NIAID. The ADCC provides a forum for coordinating research efforts for autoimmune diseases, including scleroderma, and brings together various stakeholders including the NIH, Centers for Disease Control and Prevention, Food and Drug Administration, Health Resources and Services Administration, Agency for Healthcare Research and Quality, and other public and private organizations.

The NIAMS funds two specialized centers of research investigating the genetic and environmental factors that contribute to developing scleroderma. The Institute also supports a new multidisciplinary clinical research center with a special focus on lupus and scleroderma in African Americans. In the area of childhood rheumatic diseases, the NIAMS supports a multidisciplinary clinical research center focused on juvenile scleroderma and other pediatric rheumatic diseases. Additionally, the Institute has taken a leadership role in generating research opportunities for scleroderma by supporting a national Scleroderma Family Registry and DNA Repository. The overall objective of this registry is to identify genes that influence susceptibility to the disease.

Approximately 80 percent of scleroderma patients will eventually develop some degree of lung involvement, which causes significant morbidity and mortality in scleroderma patients. In collaboration with the NIAMS, the NHLBI is supporting a multicenter clinical trial to evaluate the efficacy of oral cyclophosphamide in stabilizing or improving lung function in scleroderma patients who have active lung inflammation (alveolitis). Thirteen medical centers in the United States began enrolling patients in September 2000 and will complete enrollment within the next

few months. The steering committee for this study is planning a second treatment trial that would evaluate other immunosuppressive drugs for improving the secondary pulmonary hypertension that causes scleroderma patients to develop heart failure.

The NIAMS supports several projects which focus on new and innovative treatment options for patients with scleroderma, including: a multicenter trial to test type 1 collagen as a treatment for localized forms of scleroderma; ultraviolet phototherapy; and bone marrow stem cell transplantation. In addition, behavioral scientists supported by the Institute have found that managing pain and depression may lead to improved functioning and quality of life for patients with scleroderma. In collaboration with the NIH Office of Research on Women's Health, the NIAMS funds research aimed at uncovering the cellular and molecular processes that contribute to the development of the disease. These studies may help unravel the molecular basis of scleroderma and ultimately provide therapeutic targets.

Item

Vitiligo treatments for children – Vitiligo is an environmental and genetic auto-immune disease of unknown origin which affects about three to six million Americans. Almost fifty percent develop the disease in childhood, with the median age of onset at four years of age. In its most severe forms, patients have milky white patches covering widespread areas of the body due to the loss of pigment in these areas. Especially for young children, the physical pain caused by severe burns from the harmful effects of sunlight and the emotional pain caused by people confusing vitiligo with an infectious disease diminishes the quality of a patient's life. There are no FDA-approved treatments for children. The Committee urges NIAMS to enhance research efforts through all available mechanisms, as appropriate, to identify the causes of this disease and develop pediatric treatment options for vitiligo. (p. 92)

Action taken or to be taken

NIAMS-supported researchers have made significant advances in the field of vitiligo research. The recent discovery of two separate genetic links provides additional insight into the pathology of the disease, as well as in to the development of potential therapeutic options. Additionally, NIAMS supports an extensive portfolio addressing autoimmune disorders (conditions in which a person's immune system reacts against the body's own organs or tissues). Advances in this area will benefit the development of treatment and prevention strategies for autoimmune-related skin diseases, such as vitiligo, for both children and adults.

The Institute supports a number of projects examining the causes of vitiligo, including genetic studies of vitiligo and other hereditary diseases of pigmentation, to discover the genes that cause or predispose individuals to develop the disease. For example, NIAMS-supported researchers are gathering information from patient populations in the United States and the United Kingdom to identify genetic susceptibility for this disease. This project has recently been expanded to include minority populations, where the genetics may be different. The long-term significance of this work is the development of specific therapeutic approaches and prevention strategies.

It is important to understand not only the genetic basis but also the triggers from the environment that may lead to the development of vitiligo and other autoimmune diseases in order to make progress in prevention and treatment. To this end, the NIAMS sponsored a workshop in September 2003 on immune modulation in the treatment of skin diseases. The workshop examined immune regulation as it relates to various skin diseases and their therapies. Recommendations from this meeting will facilitate the development of future research initiatives focused on treatment strategies for a range of skin diseases, including vitiligo.

Item

Marfan syndrome - The Committee commends NIAMS for its collaboration with other institutes to support research on Marfan syndrome, a life-threatening, progressive and degenerative genetic disorder. Marfan syndrome is characterized by cardiovascular, skeletal and ocular manifestations and its cardiovascular complications can result in premature death. Insights gained from research in this area may have implications for the understanding of other connective tissue disorders, other genetically mediated diseases, and the larger population of aging adults with thoracic aneurysms from a variety of causes. The Committee encourages NIAMS to focus on research opportunities which have the potential to advance non-surgical treatment options, through all appropriate mechanisms. (p. 92)

Action taken or to be taken

Marfan syndrome is a common inherited disorder caused by a mutation in the fibrillin gene. This mutation causes the tendons, ligaments, and other connective tissues in the body to weaken. Marfan syndrome can affect the heart, skeletal system, eyes, and other organs in the body and symptoms range from mild to severe. The most serious symptoms involve the aorta, the large artery that carries blood from the heart to the rest of the body. Marfan syndrome weakens the connective tissue in the walls of the aorta, thereby increasing the chances that the artery will bulge, tear, or rupture – which can be life-threatening.

The NIAMS recently awarded a program project grant to develop a multi-site translational research program in Marfan syndrome. The long-term goal of this program is to translate basic research in matrix biology into treatment strategies for individuals with Marfan syndrome and related disorders of connective tissue. The program will utilize a comprehensive and multidisciplinary approach that integrates the scientific interest and expertise of four leading laboratories in this and related research fields. Researchers will study genetically engineered mouse models of Marfan syndrome to uncover the abnormal cellular activities that contribute to this disorder and will translate this new knowledge into more effective therapies.

The NIAMS also works closely with other NIH components in exploring research in other heritable disorders of connective tissue. It will continue its efforts to support basic, translational, and clinical research in Marfan syndrome and other heritable disorders of connective tissue in the future.

Item

Atopic dermatitis – Atopic dermatitis (AD) is one of the most common skin disorders experienced by infants and children. Over 90 percent of cases are diagnosed before the age of five. Patients with AD suffer with chronic skin inflammation and itching that disrupt sleep and reduce quality of life. An estimated 17 percent of children in the United States have atopic dermatitis, a dramatic increase above pre-1960s levels. The reason for this increase is unknown, but mirrors the increased rates of asthma and requires greater study. Of additional concern, individuals who have active or dormant AD are at high risk for serious adverse reaction to the smallpox vaccine. The Committee encourages NIAMS to work with NIAID to spearhead an initiative to encourage investigator-initiated research on AD as it relates to smallpox vaccination as well as the progression to asthma and other allergic diseases. (p. 92)

Action taken or to be taken

The NIAMS and other components of the NIH support research that is looking directly at the causes of, and treatments for, atopic dermatitis (eczema), a chronic inflammatory skin disease. For example, researchers from NIAMS are investigating Langerhans cells (cells that help protect the body from infection) to determine their role in atopic dermatitis. Other NIAMS-supported researchers are investigating the role of bacteria in triggering atopic dermatitis.

Developing new treatments for atopic dermatitis is an exciting area of research. NIAMS-funded researchers are using a mouse model of atopic dermatitis to gain insights into the cause of this disease and to evaluate the effectiveness of new treatment options. NIAMS supports research comparing the effectiveness of topical (applied directly to the skin) treatment options versus intravenous methods to treat the inflammation associated with atopic dermatitis.

The NIAMS currently supports research on atopic dermatitis related to susceptibility to eczema vaccinatum (EV), the most common life-threatening complication of the smallpox vaccination. EV occurs almost exclusively in people with a history of atopic dermatitis. The NIAMS would welcome opportunities to collaborate with NIAID to encourage investigator-initiated research on atopic dermatitis as it relates to EV and the smallpox vaccination.

Item

Burden of skin diseases - The Committee commends NIAMS for conducting a workshop on the burden of skin diseases. The participants in the workshop recommended that skin disease-specific measures be developed in order to generate data on the incidence, prevalence, economic burden and disability attributable to these diseases. The Committee encourages NIAMS to continue to work with the scientific community to implement the recommendations of the workshop participants. (p.93)

Action taken or to be taken

In September 2002, the NIAMS sponsored the “Workshop on the Burden of Skin Disease” to discuss 1) the elements that comprise the burden of skin diseases and their impact on public

health and daily living; 2) current knowledge and data-collection instruments; 3) how to access the data more effectively; and 4) future data needs and instruments for facilitating the collection of the data. The lessons learned from this workshop will serve as a paradigm for other areas – all of which share the challenge of defining the burden of a disease on an individual, the family, the workplace, and society as a whole.

The NIAMS has recently awarded a contract which will address the recommendations of the workshop participants. Researchers will determine whether or not existing skin disease databases can be used to address disease burden. During this process, gaps in data will be identified. If it is determined that existing databases cannot address the burden of skin disease appropriately, or the existing gaps cannot be addressed, recommendations will be made for the development of new instruments and database designs that could effectively address the burden of skin disease.

Item

Psoriasis – Psoriasis is a chronic, immune-mediated disease that affects more than five million Americans. A 1999 NIMH-supported study found that patients with psoriasis reported reduction in physical and mental functioning comparable to that seen in cancer, arthritis, hypertension, heart disease, diabetes, and depression. The Committee considers research on psoriasis and psoriatic arthritis important, and is pleased that NIAMS helped create a psoriasis tissue bank from which the first several psoriasis genes have been identified. The Committee encourages NIAMS to support additional research into the identification of other genes expected to play a role in psoriasis pathogenesis and to strengthen clinical research on potential therapies for psoriasis and psoriatic arthritis. (p. 93)

Action taken or to be taken

Psoriasis is a common and chronic skin disease characterized by scaling and inflammation. It affects millions of Americans, including people of all ages. The NIAMS actively supports psoriasis research to improve our understanding of the disease, develop more effective treatments, and expand our knowledge of genes that play a role in the development of this disease.

A team of NIAMS-supported researchers has recently identified two genes associated with psoriasis. The region between these two genes acts as a binding site for a protein that normally serves to regulate genes involved in immune reactions. The researchers found that when this region is altered, susceptibility to psoriasis occurs. These findings provide further progress toward understanding the cause of psoriasis in patients with a family history of the disease. This information will be used in future studies to investigate other psoriasis populations, as well as to examine other inflammatory diseases.

In September 2003, the NIAMS, in conjunction with the NIH Office of Rare Diseases, held a conference on immunomodulatory drugs in the treatment of skin diseases. The conference explored what we can learn about the development of skin diseases, including psoriasis, by looking at how new immunomodulatory drugs work. We anticipate that the insights from this

meeting will help identify scientific opportunities that may promote a better understanding of various skin diseases and how best to treat them.

Item

Mucopolysaccharidosis (MPS) – The Committee is aware of NIAMS's recent efforts with NIDDK to facilitate communication between MPS and Lysosomal Storage Disorder investigators with bone pathology and connective tissue scientists to examine problematic issues in this area of study. The Committee encourages NIAMS to enhance its efforts to directly support and collaborate with NIDDK on bone and joint diseases in MPS disorders. (p. 93)

Action taken or to be taken

The mucopolysaccharidoses consist of a group of inherited metabolic disorders caused by a deficiency of the specific lysosomal enzymes needed to break down mucopolysaccharides. Mucopolysaccharides are long chains of sugar molecules used to build connective tissues and organs in the body. When mutations occur in the genes for the enzymes involved in the normal turnover of mucopolysaccharides, excess amounts of them are stored in the body. The buildup of these sugar molecules inside cells causes various problems, including bone and joint irregularities. Progressive physical disability results from bone and joint manifestations associated with the mucuopolysaccharidosis.

The NIAMS supports a broad portfolio of basic, clinical, and translational research in bone and connective tissue biology. Broad areas of interest include skeletal development, metabolism, functional aspects of cartilage, components of connective tissues, and etiology and pathogenic mechanisms in heritable disorders of connective tissue. The Institute also supports the development of new technologies with the potential to improve treatment of skeletal disorders and facilitate the repair of trauma in the normal skeleton. These include drugs and nutritional interventions, joint replacement, bone and cartilage transplantation, and gene therapy. Advances in these fields may provide researchers examining mucopolysaccharidosis with additional information related to basic biology that may lead to the development of potential therapeutic options. Further, the NIAMS encourages highly meritorious applications in mucopolysaccharidosis research relevant to our mission, in an effort to broaden the base of inquiry in fundamental biomedical research.

FY 2005 Senate Appropriations Committee Report Language (S. Rpt. 108-345)

Item

Arthritis - Arthritis is the leading cause of disability in the United States, with 70 million Americans living with some form of the disease of chronic joint symptoms. The NIAMS is a leader in the field of arthritis research. The committee urges NIAMS to collaborate with other NIH institutes toward a cure for arthritis and related diseases. (p. 138)

Action taken or to be taken

The NIAMS, in collaboration with other NIH institutes, has taken proactive steps to advance the basic, clinical, and translational components of arthritis research. For example, NIAMS, along with other components of the NIH, is supporting research into the application of genetic factors for susceptibility and severity of arthritis. This research has the potential to identify patients most at risk of developing a particular type of arthritis so that appropriate treatment strategies can be applied before the disease progresses. Further, NIAMS funds research using mouse models to uncover the cellular and molecular processes that lead to inflammation, a common characteristic of most types of arthritis.

Quality-of-life research is an active area of interest at the NIH. To address this issue as it relates to arthritis, the NIAMS recently hosted a workshop on the role of fatigue in rheumatic disease. This workshop brought expert scientists and clinicians together to identify knowledge gaps associated with the study and treatment of fatigue in rheumatic disease, including rheumatoid arthritis and osteoarthritis, and to identify how advances in other diseases could be applied to better understand and treat fatigue. In addition to this workshop, the NIAMS, along with other components of the NIH, is involved in an initiative to develop automated instrumentation and procedures to record in a reliable way patient-reported outcomes such as pain or fatigue, which are so important in terms of quality-of-life. Other NIH-supported researchers are studying the effects of cognitive-behavioral therapy, Tai Chi (a form of movement-based meditation), and education on disease severity and mood disturbance.

Osteoarthritis (OA) is the most common form of arthritis, and it not only affects millions of Americans today, but it is also expected to affect many more people in the future as the number of elderly in our country increases. The NIAMS supports a diverse portfolio to improve our understanding of the underlying causes of osteoarthritis, improve the diagnosis and treatment of osteoarthritis, and improve the quality of life for affected individuals. For example, in collaboration with the National Institute on Aging and other NIH components, and pharmaceutical companies, NIAMS launched the Osteoarthritis Initiative, a public-private partnership that brings together new resources and commitment to help identify biomarkers of disease for OA B biological clues to increased susceptibility, early stages of disease, the course of disease, and the response of people with osteoarthritis to various therapies. This initiative should help speed drug development for OA, which is hindered by the lack of objective and measurable standards for disease progression needed for drug evaluation. Patient recruitment began in the spring of 2004. In addition to participating in the Osteoarthritis Initiative, the NIAMS has recently established the Osteoarthritis Biomarkers Network to hasten the pace of discovery of molecular biomarkers for osteoarthritis. Researchers in the United States and Sweden will share clinical, biological, and human resources. Through the network, investigators will learn more about joint destruction by identifying and monitoring biomarkers in joint, bone, and synovial tissues. This could provide the clues needed to define the stages of disease on a more consistent and reliable basis.

Item

Bone and Cartilage Diseases - The Committee urges NIAMS to explore new avenues for cell and gene-based therapies for the treatment of bone and cartilage diseases, such as osteoporosis,

Paget's disease, and osteogenesis perfecta. Identifying new targets for enhancing bone formation and blocking bone destruction should be a major focus, with studies that integrate basic and clinical approaches regarding bone forming cell development. (p. 138)

Action taken or to be taken

NIAMS-supported researchers are actively exploring the potential use of cell- and gene-based therapies for the treatment of bone and cartilage diseases. For example, researchers have recently used a combination of mouse breeding and genetic technology to identify a gene that strongly influences peak bone mass in mice. The gene, which is present in humans as well as mice, was not previously known to be involved in bone biology, and hence represents a promising new target for development of drugs that could prevent or reverse bone loss.

Other NIAMS-supported researchers are focusing on basic and applied stem cell research. For example, researchers are investigating the growth factors and hormones that influence how stem cells develop, which should guide the development of therapies in bone diseases. Another group of researchers is using stem cell therapy for diseases of bone in a mouse model. This project uses a mouse model of osteogenesis imperfecta to evaluate possibilities of regeneration or repair of bone marrow using mouse stem cells. Other NIAMS-supported investigators will follow programmed cell activity -- specifically, the life and death of a cell -- and show how that activity generates a form of stem cells that are a factor in maintaining adult bone mass. Researchers have also created a genetically modified mouse that develops lesions similar to those of Paget's disease. This mouse model may prove to be a valuable model of the disease process. Finally, other NIAMS-supported researchers have demonstrated that a gene transferred into human cells can be targeted to the collagen gene that is defective in most types of osteogenesis imperfecta.

Osteoarthritis is a disease of wear and tear on the joints. Its progression causes severe pain that results from degraded cartilage, broken-down bone (which creates bony spurs), and sometimes thickened and inflamed synovial tissue. To hasten the pace of discovery of molecular biomarkers for osteoarthritis, the NIAMS has established the Osteoarthritis Biomarkers Network, a collaborative research program between researchers in the United States and Sweden. For the first time, researchers who have been individually studying osteoarthritis biomarkers -- molecular indicators of disease presence and progression -- will share clinical, biological, and human resources. Through the network, investigators will learn more about joint destruction by identifying and monitoring biomarkers in joint, bone, and synovial tissues. This could provide the clues needed to define the stages of disease on a more consistent and reliable basis. The Network complements the ongoing work of the Osteoarthritis Initiative, a public-private partnership that brings together new resources and commitment to help identify biomarkers of disease in osteoarthritis.

Item

Lupus – The committee is aware of the importance of lupus susceptibility genes. Voluntary health organizations have established a collaboration among many individual research teams throughout the country to accelerate the search for these genes. The committee urges the

Institute to pursue this collaboration and to provide increased funding so that sufficiently large patient cohorts can be developed that will facilitate research in this area. Because lupus is a disorder that disproportionately affects women of African American, Hispanic and Asian ancestry, appropriate numbers of samples from these populations should be included in these cohorts. The Committee also urges the Institute to consider the importance of creating repositories that might aid research in the genetic aspects of lupus. (p. 138)

Action taken or to be taken

The NIAMS is continuing to enhance its research activities in lupus through a multitude of efforts. For example, the NIAMS supports a large lupus registry and repository designed to accelerate the search for lupus susceptibility genes. This registry collects and updates clinical, demographic, and laboratory data on patients with lupus and their families. Researchers analyze DNA samples to search for the presence of genetic markers. About one-third of the families studied are African American. In addition, researchers are increasing the number of Mexican American and Puerto Rican families affected by lupus who are included in the Lupus Registry and Repository.

Researchers supported by the NIAMS, in collaboration with other components of the NIH – including the National Institute of Allergy and Infectious Diseases, National Center on Minority Health and Health Disparities, and the Office of Research on Women's Health – have discovered a genetic "signature" present in some patients with lupus who develop life-threatening complications such as blood disorders, central nervous system damage, and kidney failure. These findings provide strong support for developing new therapies to block the affected pathways in patients with severe lupus, as well as for identifying patients most likely to benefit from these new therapies. Other NIAMS-supported researchers have found two gene forms that appear more frequently in African American female lupus patients. African Americans with lupus have greater morbidity and mortality primarily due to renal (kidney) disease.

To coordinate Federal efforts in lupus research and education, the NIAMS leads the Lupus Federal Working Group. It is comprised of representatives from all relevant HHS agencies and other Federal departments having an interest in lupus. Additionally, the NIAMS leads the new Lupus Biomarkers Working Group, which complements the activities of the Lupus Federal Working Group. In the fall of 2003, the Lupus Biomarkers Working Group invited a group of experts from the lupus research community to discuss how to establish new strategies for developing and validating biomarkers for lupus. These biomarkers will be used in clinical settings to facilitate the process of making new therapies available to patients. Participants included clinical and basic scientists from the lupus research community, as well as representatives of the NIH, Food and Drug Administration, and voluntary organizations.

In the fall of 2003, national leaders in lupus research came together to discuss the latest scientific opportunities at the "Lupus Today: Research Into Action" scientific conference. As a cosponsor for this conference, the NIAMS invited leading lupus researchers to discuss the latest scientific discoveries and what they mean for the current and future management of lupus.

Item

Marfan Syndrome – The Committee commends NIAMS and its collaborative efforts with other institutes to provide vital support for research on Marfan syndrome, a life-threatening, progressive and degenerative genetic disorder. The Committee urges NIAMS to focus on research opportunities that have the potential to advance non-surgical treatment options, through all available mechanisms, as appropriate. (p. 139)

Action taken or to be taken

Please refer to page NIAMS-33 of this document for NIAMS' response to this significant item regarding Marfan syndrome.

Item

Metabolic Bone Diseases – The Committee encourages NIAMS to support trans-NIH research into all aspects of genetics and gene therapies for the treatment of metabolic bone diseases, the role of environmental and lifestyle factors in bone disease, the effects of depression and cardiovascular disease on bone disease, the impact of mechanical loading of bone, translational research to bring the recent exciting basic discoveries about bone in to clinical practice, and on bone health and osteoporosis in special groups, such as non-Caucasian ethnic groups. (p. 139)

Action taken or to be taken

Please refer to page NIAMS-29 of this document for NIAMS' response to this significant item regarding bone diseases.

Item

Mucopolysaccharidosis [MPS] – The Committee is aware of recent efforts with NIDDK to facilitate communication between MPS and Lysosomal Storage Disorder investigators with bone pathology and connective tissue scientists to examine problematic issues in this area of study. Research in the underlying pathophysiology of bone and joint lesions, the gene mutations and substrates that are stored and potential therapeutic approaches are of interest to the Committee. The Committee encourages NIAMS to enhance its efforts to directly support and collaborate with NIDDK on bone and joint diseases in MPS disorders. (p. 139)

Action taken or to be taken

Please refer to page NIAMS-36 of this document for NIAMS' response to this significant item regarding mucopolysaccharidosis.

Item

Scleroderma – The Committee is encouraged by NIAMS's growing interest in scleroderma, a chronic and progressive disease that predominantly strikes women. Scleroderma is disfiguring

and can be life-threatening and effective treatments are lacking. The Committee encourages NIAMS to collaborate with other institutes, including NHLBI, NIDDK, NIAID, and NIDCR to generate additional research opportunities for scleroderma to identify genetic risk factors and safe and effective treatments. (p. 139)

Action taken or to be taken

Please refer to page NIAMS-31 of this document for NIAMS' response to this significant item regarding scleroderma.

Item

Tuberous Sclerosis Complex - Tuberous sclerosis complex, or TSC is a genetic disorder that triggers uncontrollable tumor growth in multiple organs of the body, including the skin. The Committee strongly encourages NIAMS to support programs examining the molecular and cellular basis of dermatological lesions in TSC as well as the development of non-surgical treatment for skin manifestations. (p. 139)

Action taken or to be taken

Tuberous sclerosis complex is a rare and genetic, neurological disorder primarily characterized by seizures, mental retardation, and skin and eye lesions. Small benign tumors may grow on the face and eyes, as well as in the brain, kidneys, and other organs. Individuals with tuberous sclerosis complex may experience none or all of the associated symptoms with varying degrees or severity.

The NIAMS supports a broad portfolio of skin disease research that could increase the understanding of the skin manifestations of tuberous sclerosis complex. Fibromas – benign tumors containing fibrous tissues – are commonly seen in patients with the disease. NIAMS-supported researchers are currently studying collagen biochemistry and the function of collagen-producing cells. This research will provide insight on the basic biology of fibroma development. Other NIAMS-supported researchers are examining new topical and laser-based treatments for acne and keloids (skin overgrowths of dense fibrous tissues). This research would provide researchers with a background for developing non-surgical treatment options for patients with tuberous sclerosis complex. Additionally, the NIAMS encourages highly meritorious applications in mission-related research that is directly related to tuberous sclerosis complex, in an effort to broaden the base of inquiry in fundamental biomedical research.

NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2005 Amount Authorized	FY 2005 Appropriation	2006 Amount Authorized	2006 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$495,569,000	Indefinite	$497,544,000
National Institute of Arthritis and Musculoskeletal and Skin Diseases	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	15,588,000		15,519,000
Total, Budget Authority				511,157,000		513,063,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.

NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1997	$243,169,000 2/	$257,637,000 2/	$247,731,000	$257,003,000 3/
1998	258,932,000 2/	265,458,000 2/	268,210,000	274,760,000
1999	290,176,000 2/4/	296,688,000	304,320,000	308,164,000
Rescission				(204,000)
2000	309,953,000 2/	333,378,000	350,429,000	351,840,000
Rescission				(1,872,000)
2001	363,479,000 2/	400,025,000	401,161,000	396,604,000
Rescission				(144,000)
2002	443,565,000	440,144,000	460,202,000	448,865,000
Rescission				(617,000)
2003	485,851,000	485,851,000	489,324,000	489,324,000
Rescission				(3,181,000)
2004	502,778,000	502,778,000	505,000,000	504,300,000
Rescission				(3,234,000)
2005	515,378,000	515,378,000	520,900,000	515,378,000
Rescission				(4,221,000)
2006	513,063,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
3/ Excludes enacted administrative reductions of $108,000.
4/ Reflects a decrease of $877,000 for the budget amendment for bioterrorism.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Office of the Director	52	50	50
Extramural Programs	32	37	37
Intramural Research Program	136	133	133
Total	220	220	220
FTEs supported by funds from Cooperative Research and Development Agreements	(0)	(0)	(0)

FISCAL YEAR	Average GM/GS Grade
2002	10.2
2003	10.7
2004	11.4
2005	11.4
2006	11.4

NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Detail of Positions

GRADE	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
ES	2	2	2
Subtotal	2	2	2
Total - ES Salary	$286,833	$297,948	$305,843
GM/GS-15	19	19	19
GM/GS-14	17	17	17
GM/GS-13	23	23	23
GS-12	27	27	27
GS-11	18	18	18
GS-10	1	1	1
GS-9	12	12	12
GS-8	10	10	10
GS-7	12	12	12
GS-6	2	2	2
GS-5	2	2	2
GS-4	1	1	1
GS-3	2	2	2
GS-2	0	0	0
GS-1	0	0	0
Subtotal	146	146	146
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	0	0	0
Director Grade	2	2	2
Senior Grade	0	0	0
Full Grade	0	0	0
Senior Assistant Grade	0	0	0
Assistant Grade	0	0	0
Subtotal	2	2	2
Ungraded	62	62	62
Total permanent positions	150	150	150
Total positions, end of year	212	212	212
Total full-time equivalent (FTE) employment,end of year	220	220	220
Average ES salary	$143,417	$148,974	$152,922
Average GM/GS grade	11.4	11.4	11.4
Average GM/GS salary	$72,626	$76,239	$79,098